Bacterial meningitis in the United States 1998 - 2007

Background

- rate of bacterial meningitis declined by 55% after introduction of the *Haemophilus influenzae* type b conjugate vaccins
- recent measures:
  - pneumococcal conjugate vaccine
  - universal screening of pregnant women for group B Streptococcus

MC Thigpen et al. N Engl J Med 2011, 364, 2016-25

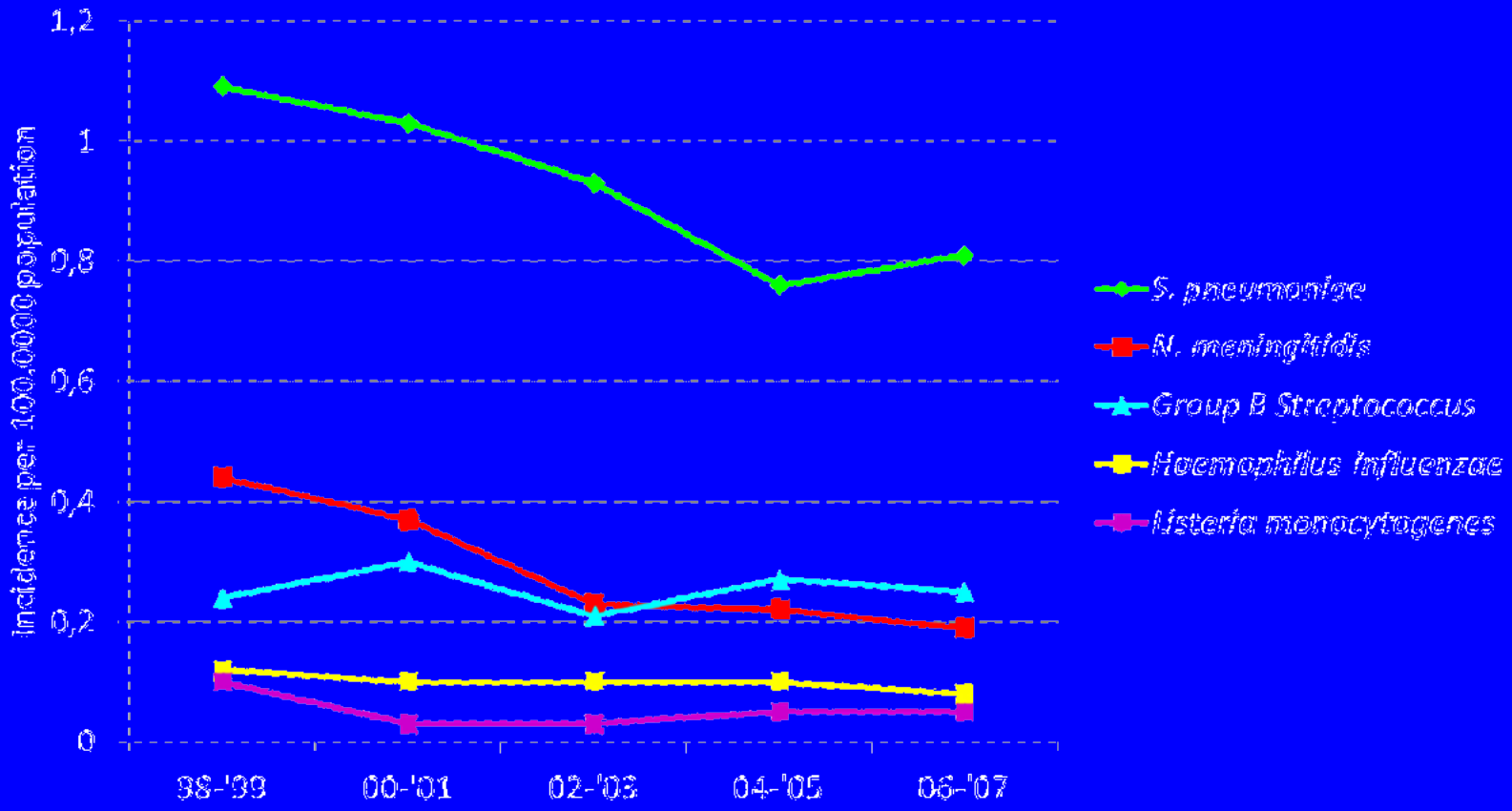
Bacterial meningitis in the United States

- <u>methods</u>:
  cases of bacterial meningitis among 17.4 million persons during 1998-2007
- <u>results</u>:

	case fatality rate %	incidence rate %
all pathogens (N=3188)	14.8	-31
S. pneumoniae (N=1813)	17.9	-76 (PCV7 serotypes: -92, non-PCV7 serotypes: +61)
N. meningitidis (N=549)	10.1	-53
Streptococcus group B (N=384)	11.1	+0.01
H. influenzae (N=187)	7	-35
L. monocytogenes (N=105)	18.1	-46

Bacterial meningitis in the United States 1998 – 2007 (3188 patients – 17,383,935 population)

1. Incidence-pathogen



Bacterial meningitis in the United States 1998 – 2007 (3188 patients – 17,383,935 population)

2. Incidence-age groups

	'98-'99	'00-'01	'02-'03	'04-'05	'06-'07
<2mo	73.5	88.3	56.6	77.3	80.7
2-23 mo	14.2	11.49	6.6	6.9	6.9
2-10y	1.5	1.48	0.9	1.07	0.56
11-17y	1.03	0.87	0.6	0.56	0.43
18-34y	0.99	0.86	0.7	0.76	0.66
35-49y	1.23	1.3	1.08	0.91	0.95
50-64y	2.15	1.8	2.09	1.79	1.73
≥65	2.64	2.2	2.21	1.51	1.92

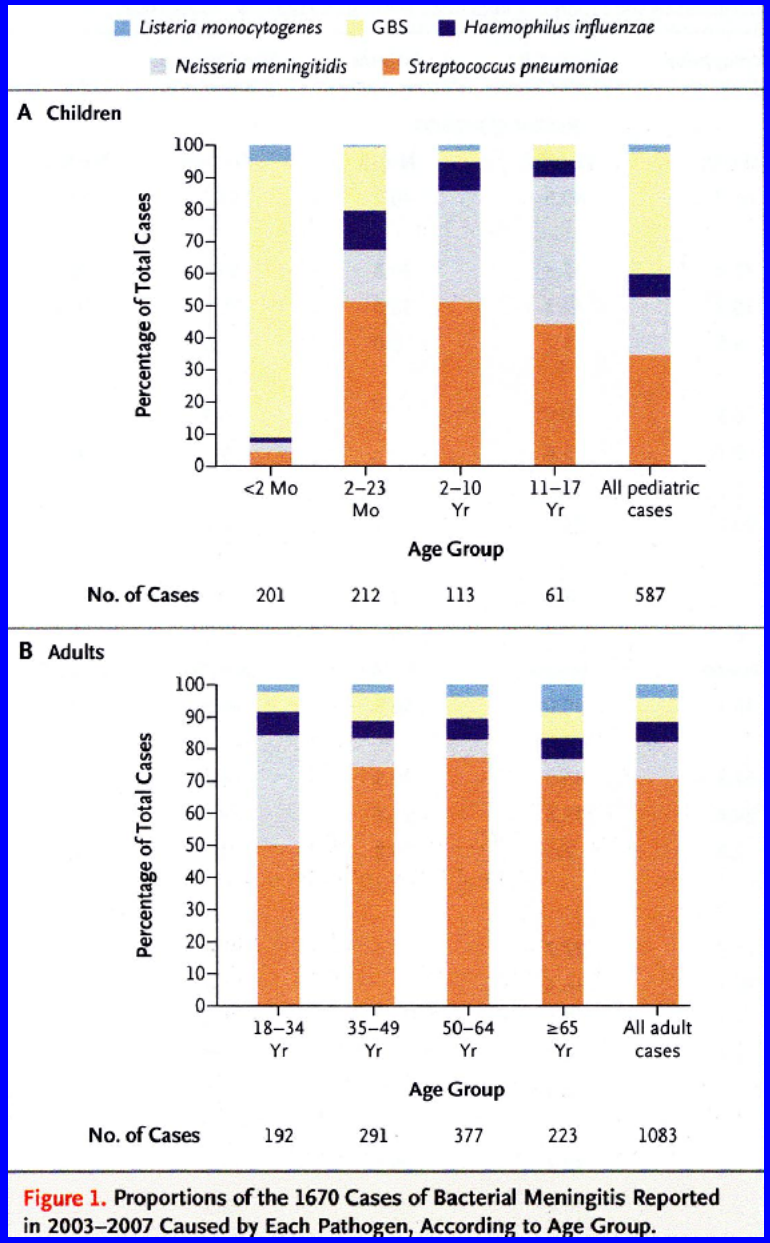


Figure 1. Proportions of the 1670 Cases of Bacterial Meningitis Reported in 2003–2007 Caused by Each Pathogen, According to Age Group.

Conclusions for bacterial meningitis in United States 1998 - 2007

- rates of bacterial meningitis have decreased since 1998 in USA primarily due to declines in rate of *S. pneumoniae* meningitis → use of PCV7 (introduced in 2000)
- no decrease among infants under 2 months of age, major organism remains Group B Streptococcus (late onset disease)
- overall incidence of *N. meningitidis* changed by -58%
  serogroup B = -55%, C = -65%, Y = -55%
  (use of quadrivalent (A, C, W_{135} and Y) meningococcal vaccin = MCV4 and MPSV4)
- overall incidence rate of *H. influenzae* changed by -35% (Hib conjugate vaccin introduced in 1990)
- overall incidence rate of *L. monocytogenes* changed by -46% (decreased consumption of high-risk foods?)

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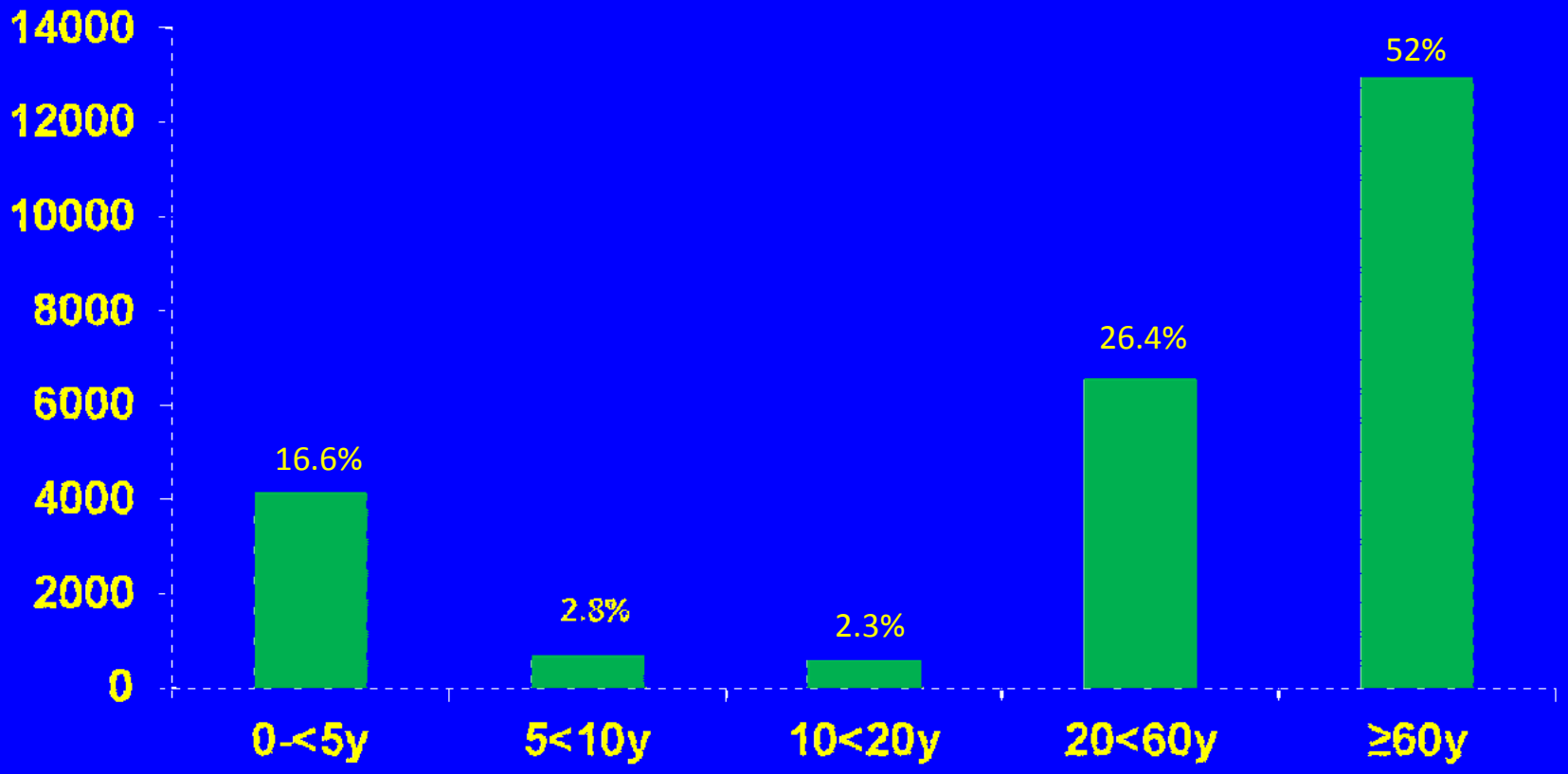
Overall incidence rates of bacterial meningitis, stratified according pathogen in United States and Belgium (1998-2007)

	1998		2007	
	USA	Belgium	USA	Belgium
Streptococcus pneumoniae	1.09	0.61	0.81	**0.7**
Neisseria meningitidis	0.44	0.61	0.19	**0.9**
Haemophilus influenzae	0.12	0.06	0.08	0
Listeria monocytogenes	0.1	0.04	0.05	0.04

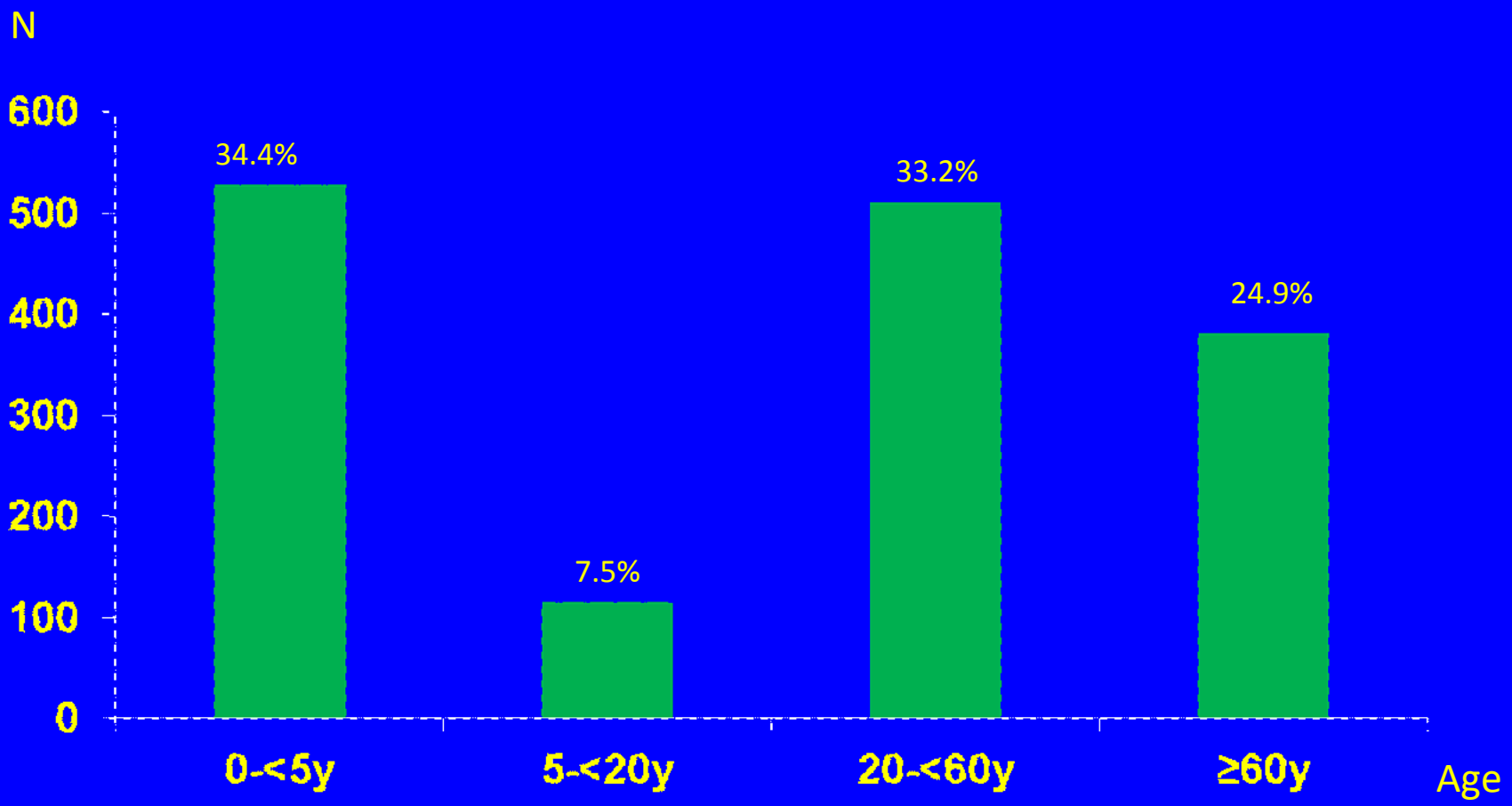
Clinical source of 31284 pneumococci (Belgium 1980-2010)

blood and pleural fluid	25349	(81.0)
middle ear aspirates	3582	(11.4)
cerebrospinal fluid	1580	(5.1)
various body fluids	773	(2.5)

Age distribution of 24887 patients with pneumococcal bacteraemia (Belgium 1980-2010)

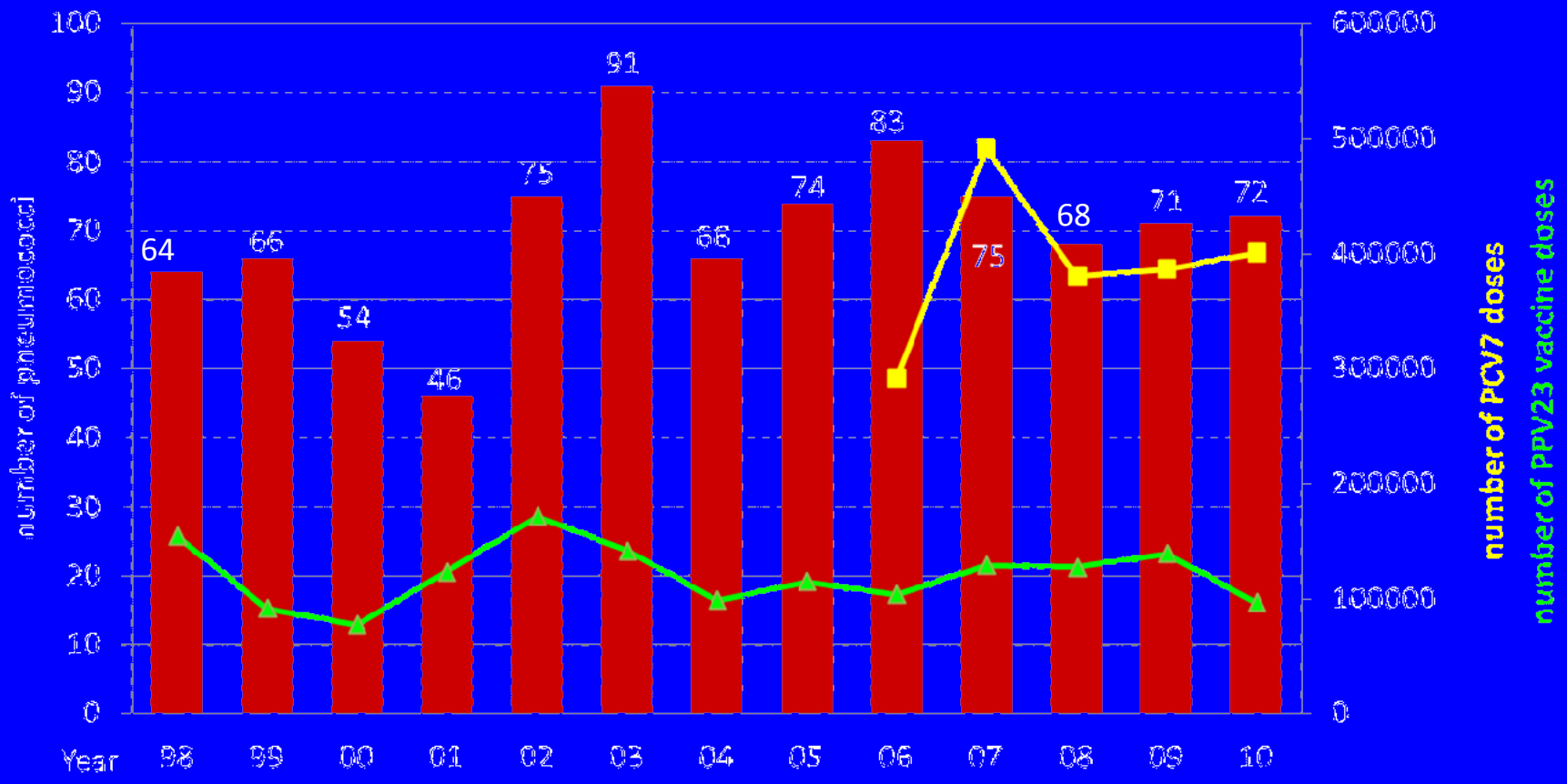


Age distribution of 1535 patients with pneumococcal meningitis (Belgium 1980-2010)



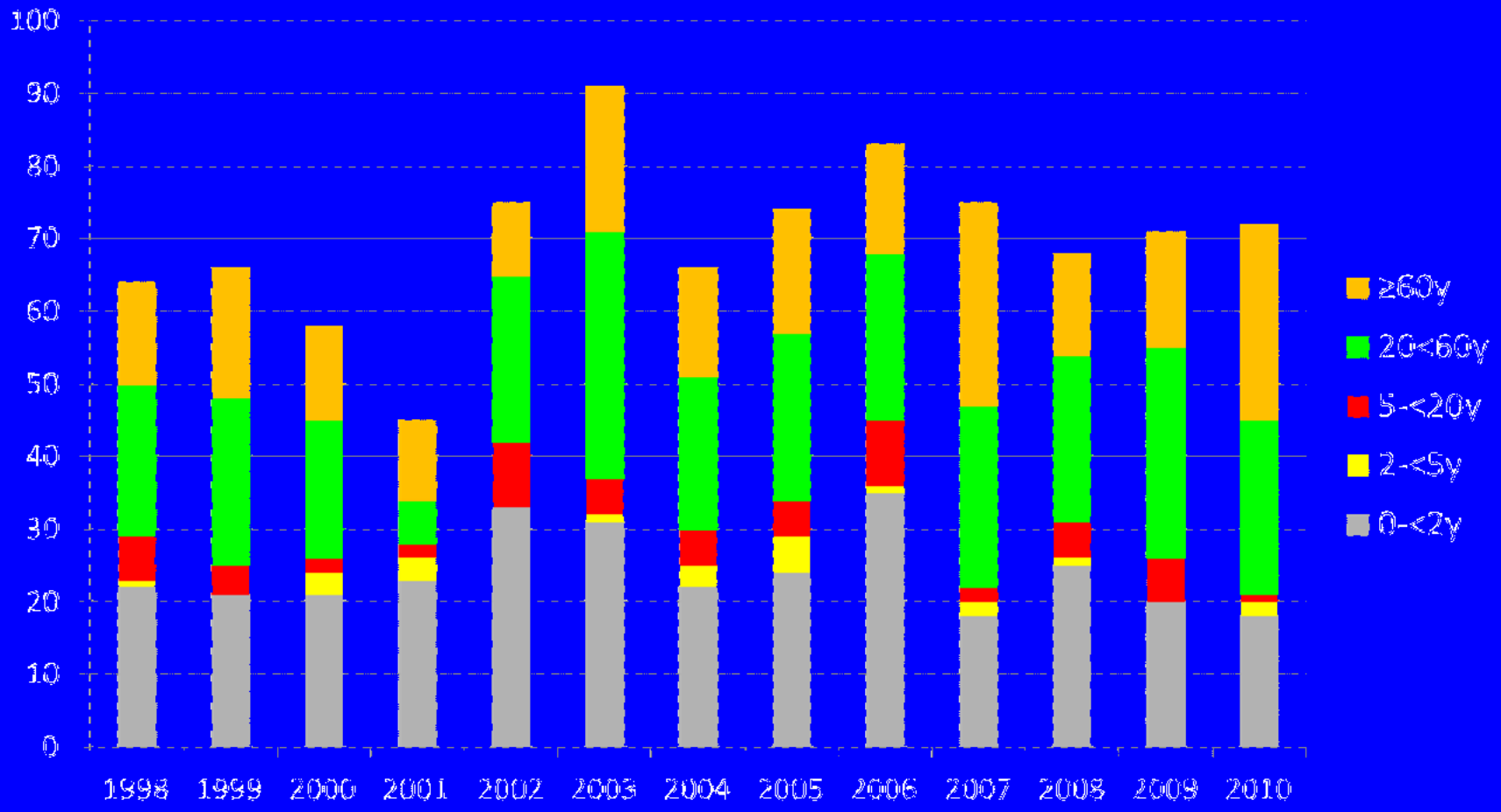
JV-11

Evolution of number of pneumococci (N=905) isolated from cerebrospinal fluid (Belgium 1998 - 2010)

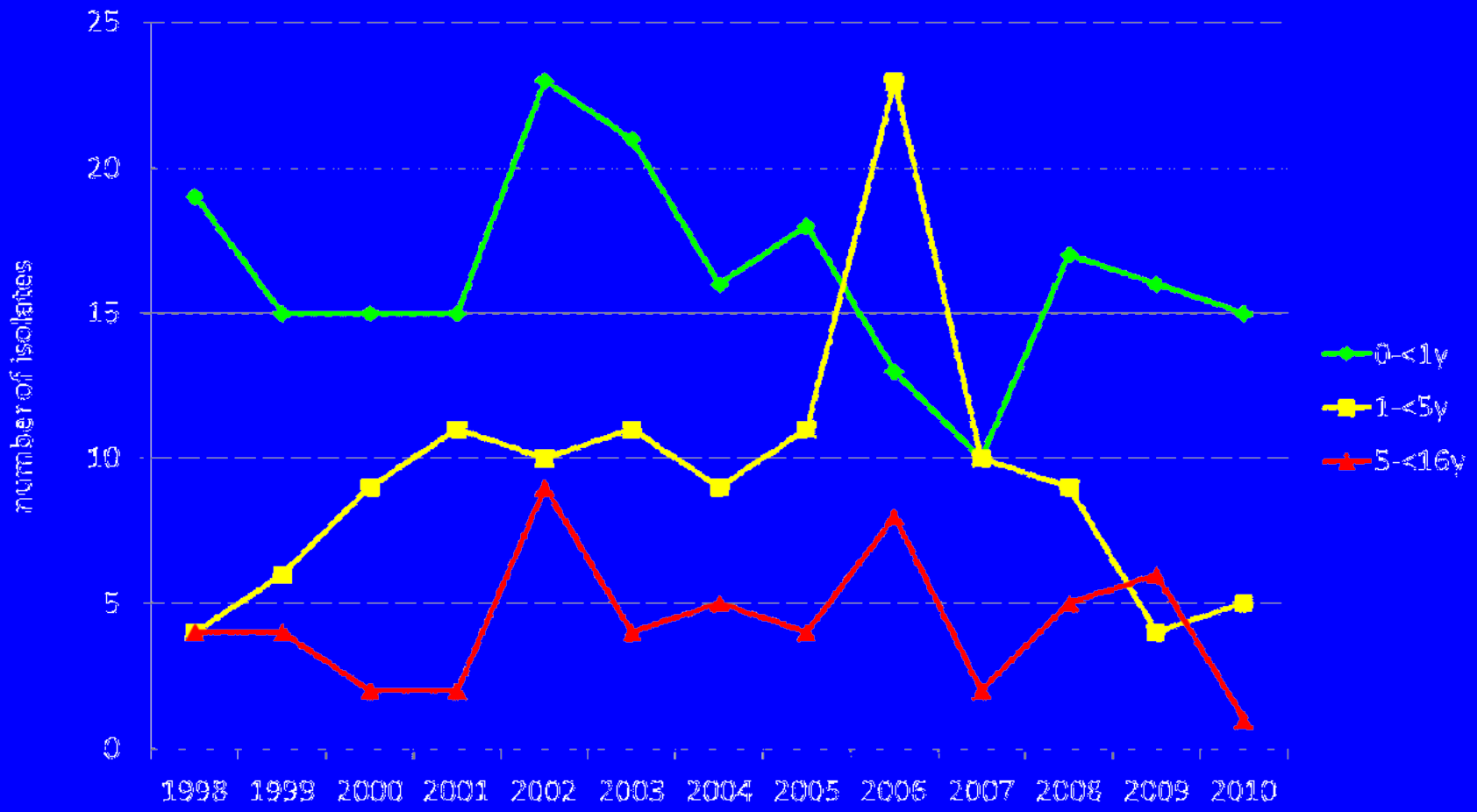


N° of participating laboratories	103	105	102	99	108	113	104	103	116	108	107	109	109

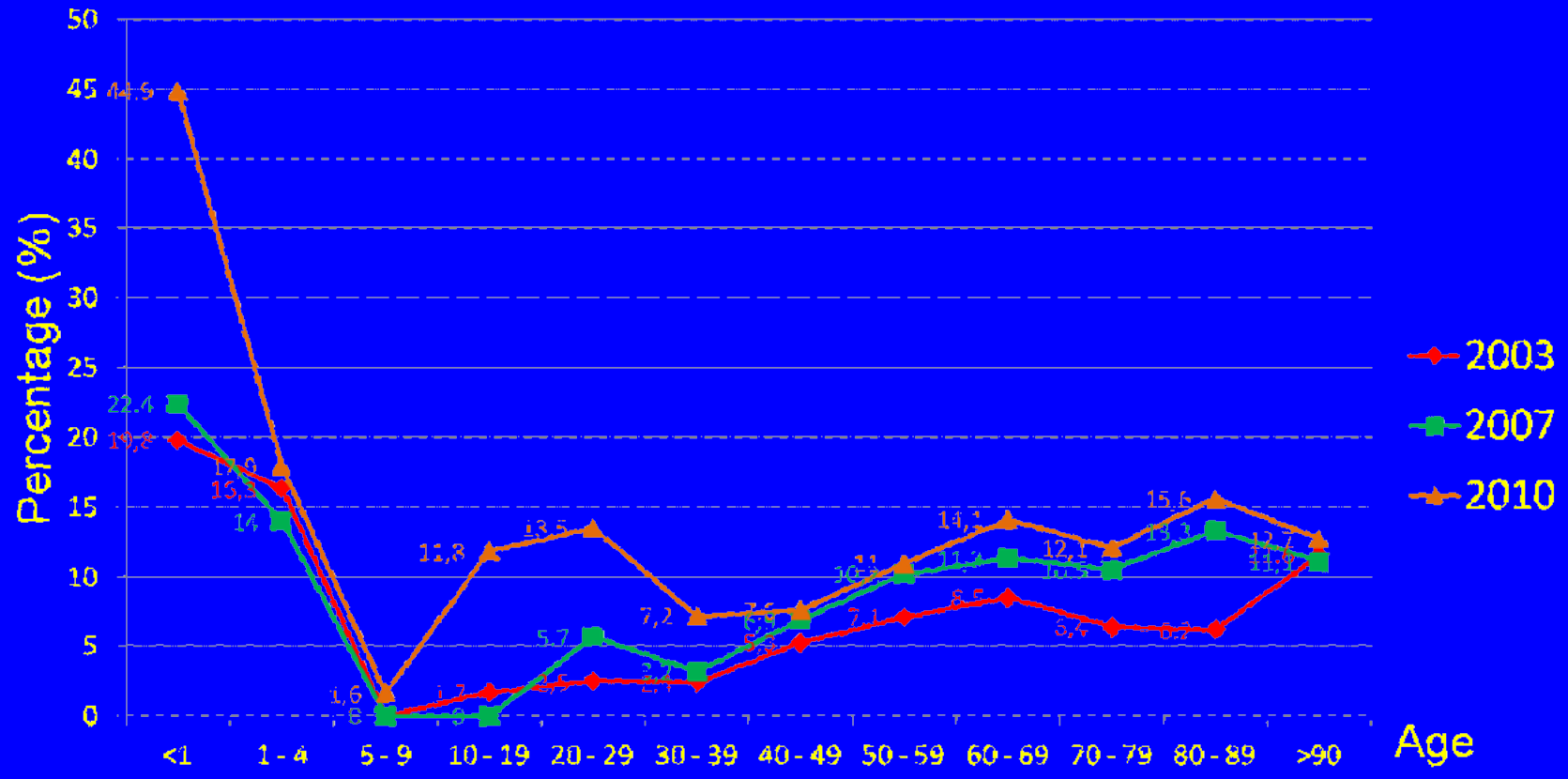
Evolution of number of pneumococci isolated from cerebrospinal fluid in different age groups (Belgium 1998 - 2010)



Evolution of number of pneumococci isolated from cerebrospinal fluid in children (Belgium 1998 – 2010)



Percentage of serogroup 19 blood culture isolates in different age groups in Belgium (2003, 2007 and 2010)



N° 2003	101	196	46	56	40	101	112	155	177	279	192	69
N° 2007	58	178	58	32	52	92	116	176	203	239	225	63
N° 2010	98	178	61	34	37	110	131	218	241	307	294	55

Predominant (>5%) capsular types of 905 *S. pneumoniae* in cerebrospinal fluid (Belgium, 1998-2010)

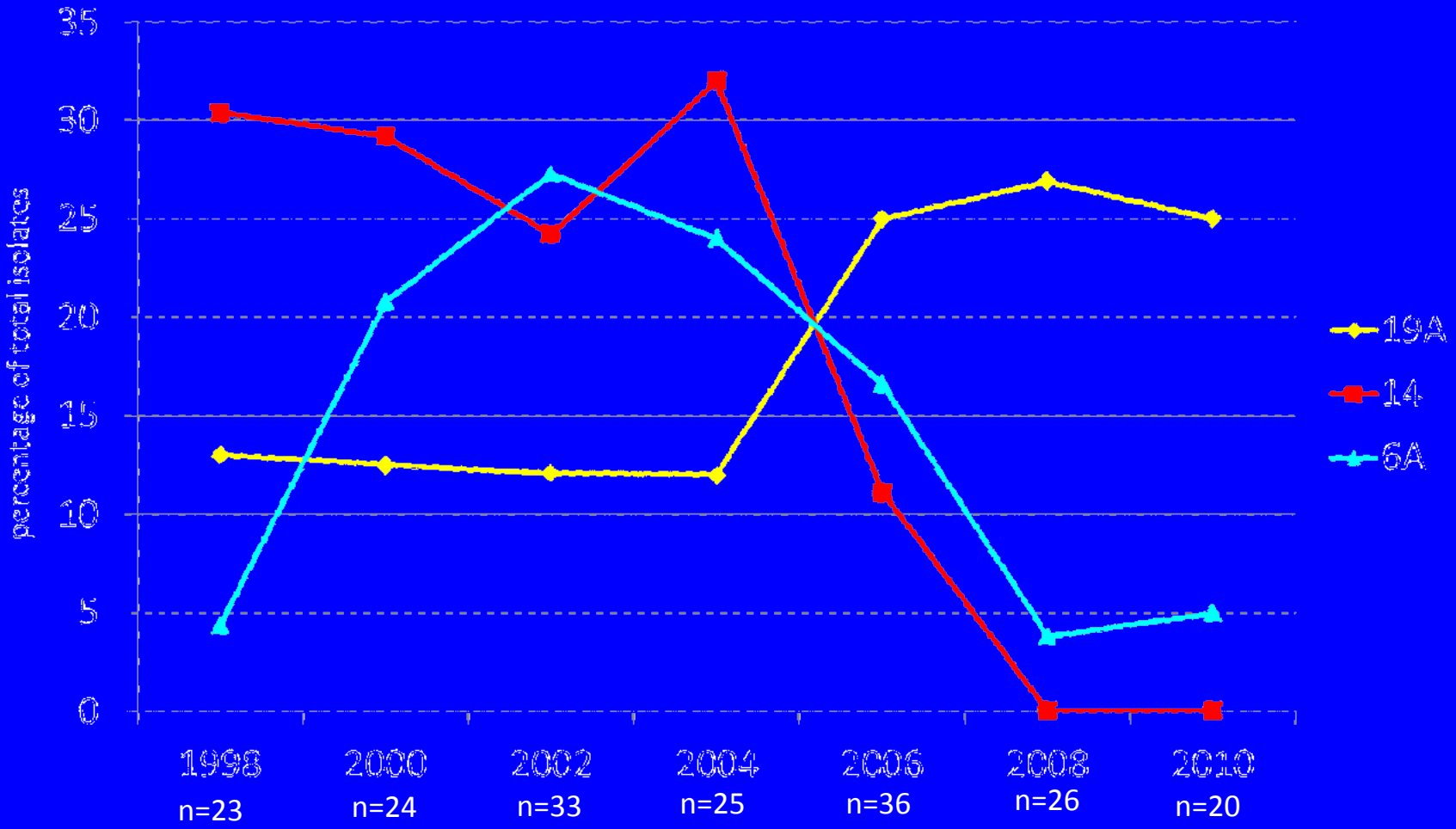
capsular group type	N	(%)
19 (>90% 19A)	131	14.5
6 (67% 6A, 30% 6B*)	98	10.8
14*	86	9.5
23 (>90% 23F*)	64	7.1
9 (>90% 9V*)	61	6.7
7 (>90% 7F)	58	6.4
18 (>90% 18C*)	50	5.5

*included in 7 valent vaccine

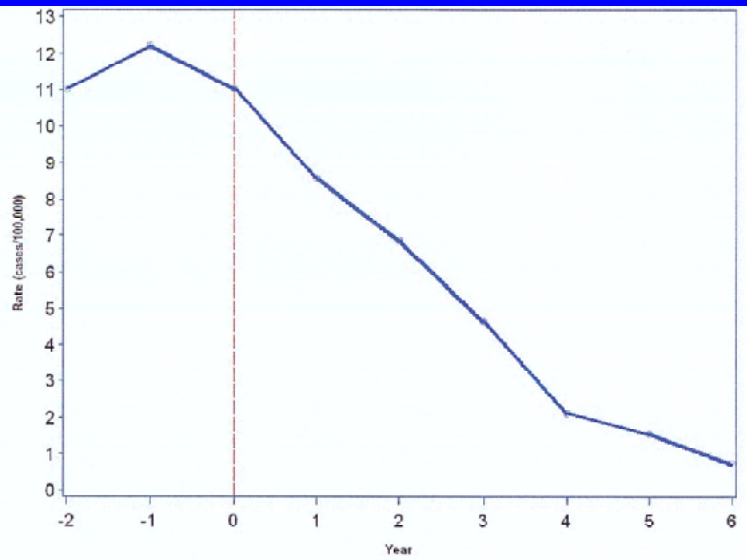
Pneumococcal conjugate vaccines

- 7-valent vaccine (PREVENAR)
  - 2 µg of 6 capsular polysaccharides: 4, 9V, 14, 18C, 19F, 23F
    4 µg of polysaccharide 6B
  - conjugated to 20 µg *C. diphtheriae* CRM_{197} protein
- 10-valent vaccine (SYNFLORIX)
  - 1 µg of 7 capsular polysaccharides: **1**, **5**, 6B, **7F**, 9V, 14, 23F
  - 3 µg of 3 capsular polysaccharides: 4, 18C, 19F
  - conjugated to 9-16 µg Protein D *Haemophilus influenzae* or 10 µg (Tetanus anatoxine (18C) or 6 µg *C. diphtheriae* anatoxine (19F)
- 13-valent vaccine (PREVENAR 13)
  - 13 capsular polysaccharides: 1, **3**, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, **19A**, 19F, 23F
  - conjugated to 20 µg *C. diphtheriae* CRM_{197} protein

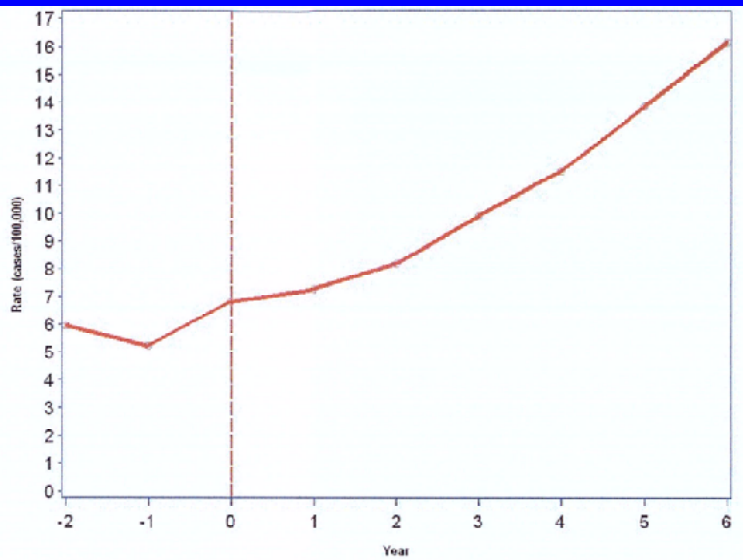
Evolution of pneumococcal capsular type 6A, 14 and 19A of *S. pneumoniae* in cerebrospinal fluid in children <5 yr (Belgium, 1998-2010)



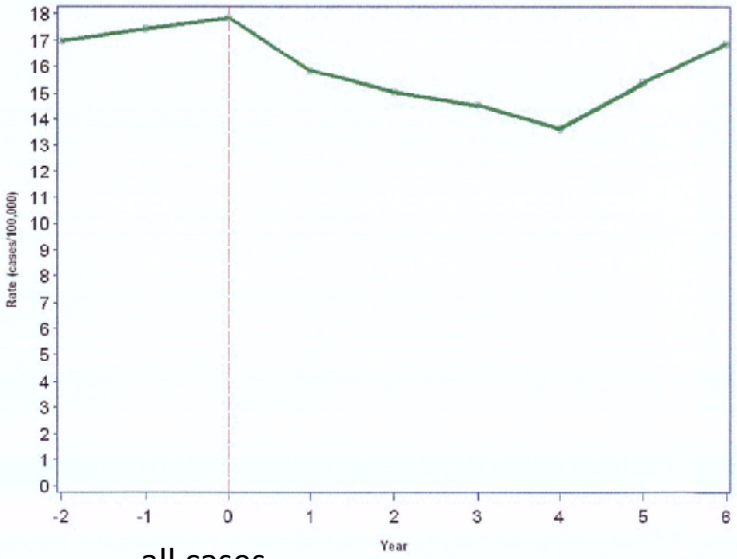
Overall IPD Rates, <5 y (Belgium)



PCV 7 serotypes



Non PCV 7 serotypes



all cases

*Values above graphs are rate ratios

2

Penicillin and cefotaxime breakpoints (mg/L) *Streptococcus pneumoniae*

CLSI (January 2011, Vol 31)

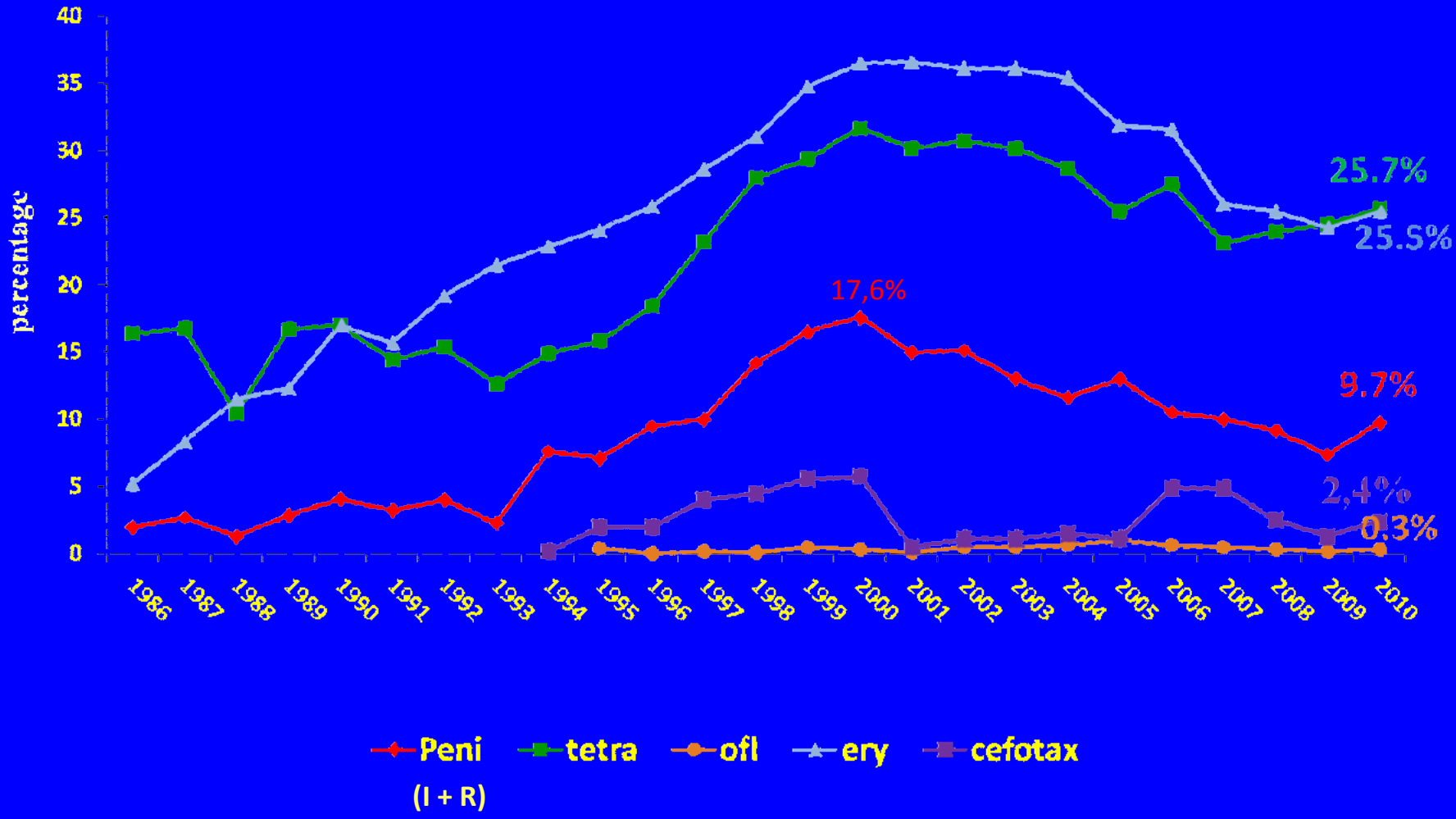
Penicillin	S	I	R
parenteral non-meningitis	≤ 2	4	≥ 8
parenteral meningitis	≤ 0.06		≥ 0.12
oral	≤ 0.06	0.12 - 1	≥ 2

Cefotaxime			
Meningitis	≤ 0.5	1	≥ 2
Non-meningitis	≤ 1	2	≥ 4

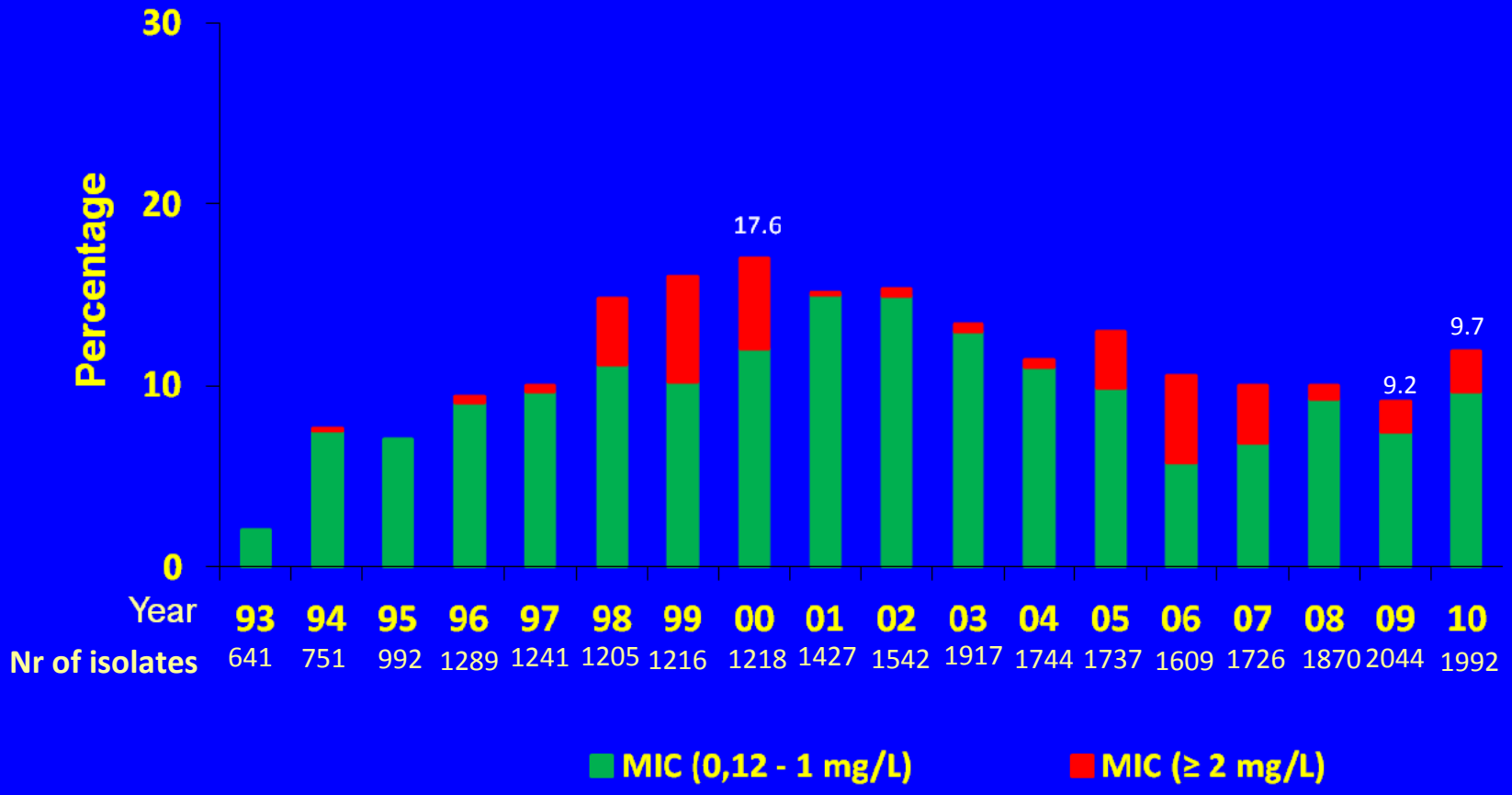
EUCAST (Table V.1.3 2011-01-05)

Benzylpenicillin (pneumoniae)	≤ 0.06		>2 (1.3g x 4/d → ≤ 0.5 mg/L) (2.4g x 4/d → ≤ 1 mg/L) (2.4g x 4/d →≤ 2mg/L)
Benzylpenicillin (meningitis)	≤ 0.06		≥ 0.12

Evolution of antibiotic resistance (%) in invasive *S. pneumoniae* isolates (Belgium 1986-2010)



Evolution of penicillin-resistance in invasive isolates of *S. pneumoniae* (Belgium 1993-2010)



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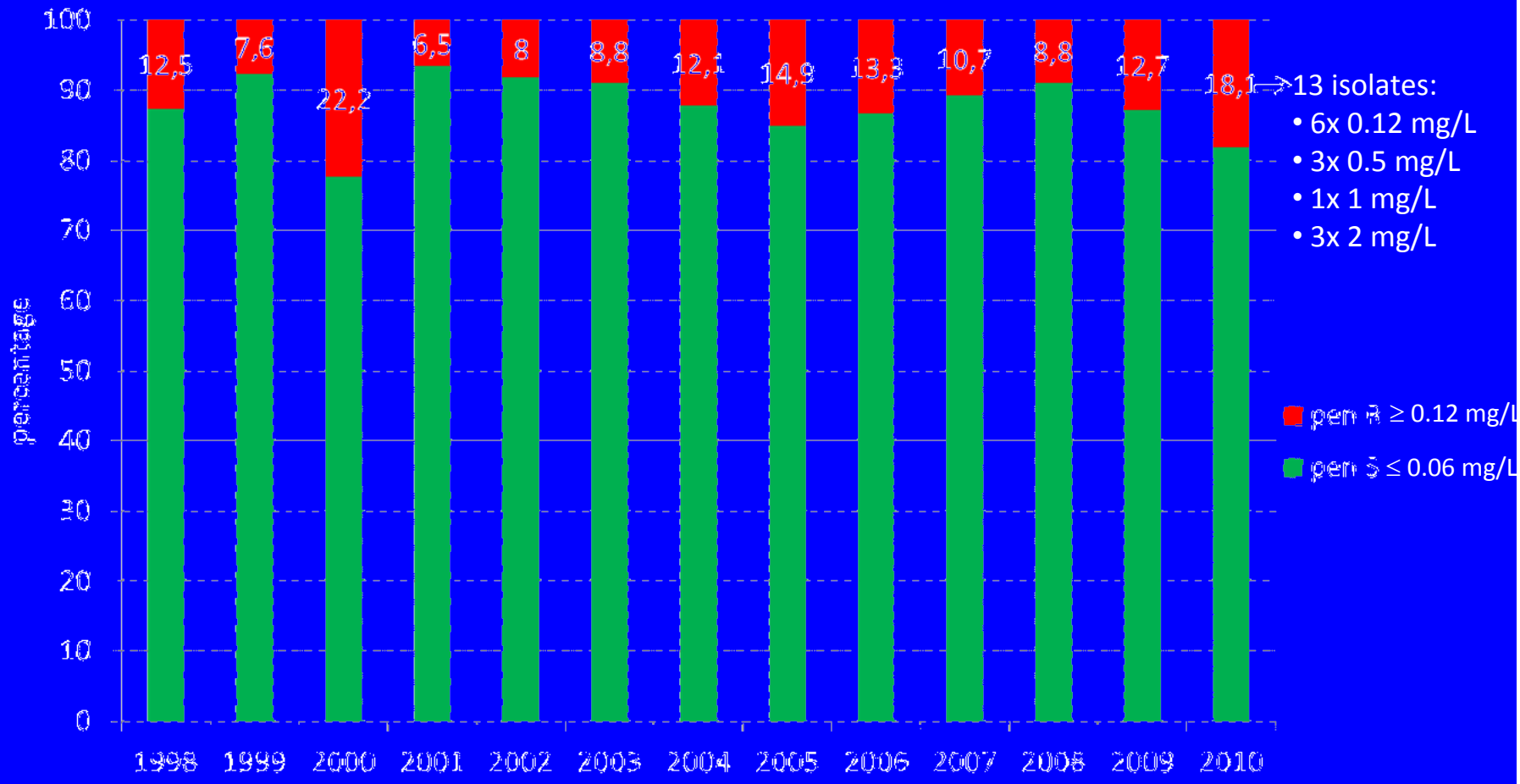
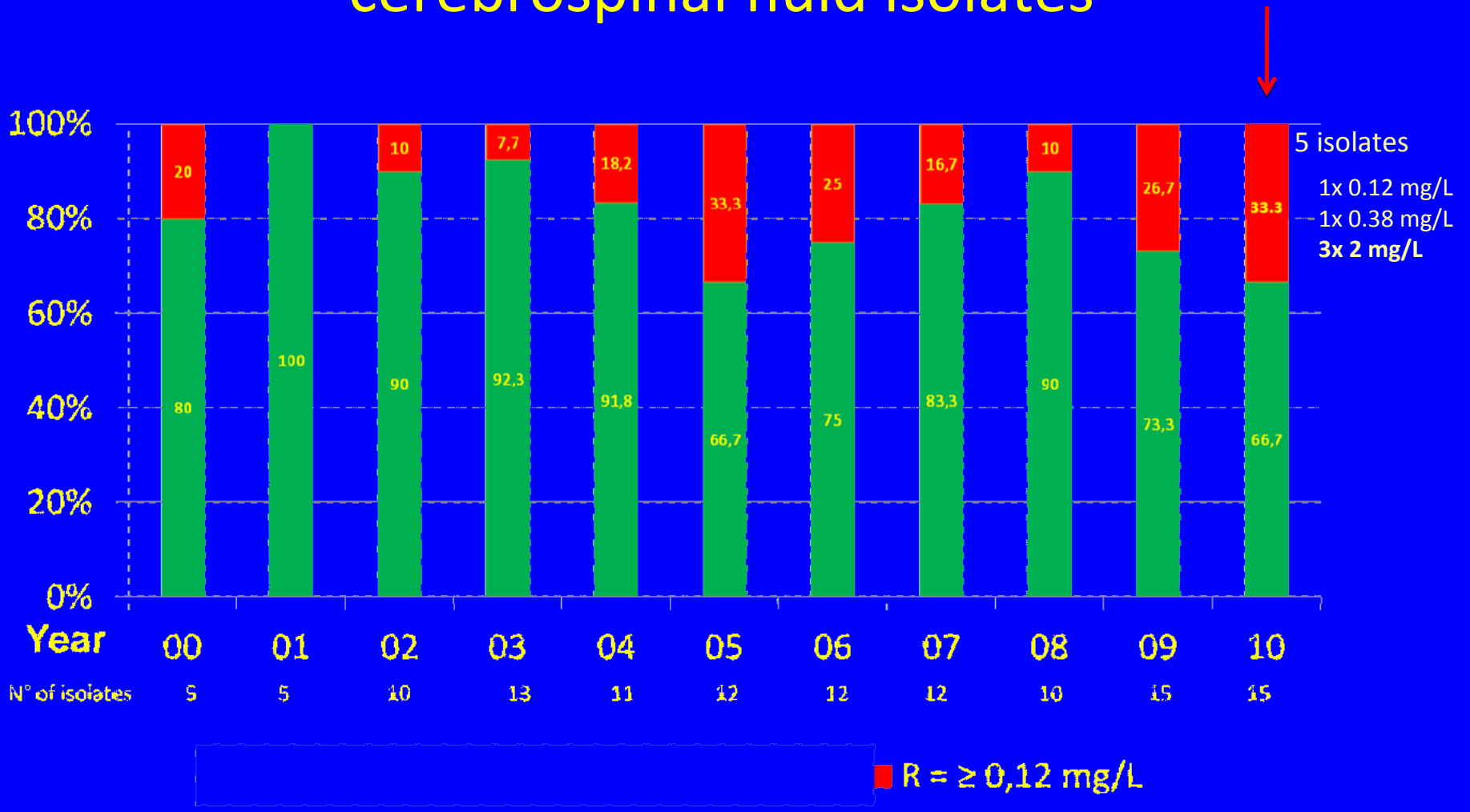
Evolution of penicillin-resistance in cerebrospinal fluid isolates of *S. pneumoniae* (Belgium 1998 – 2010)

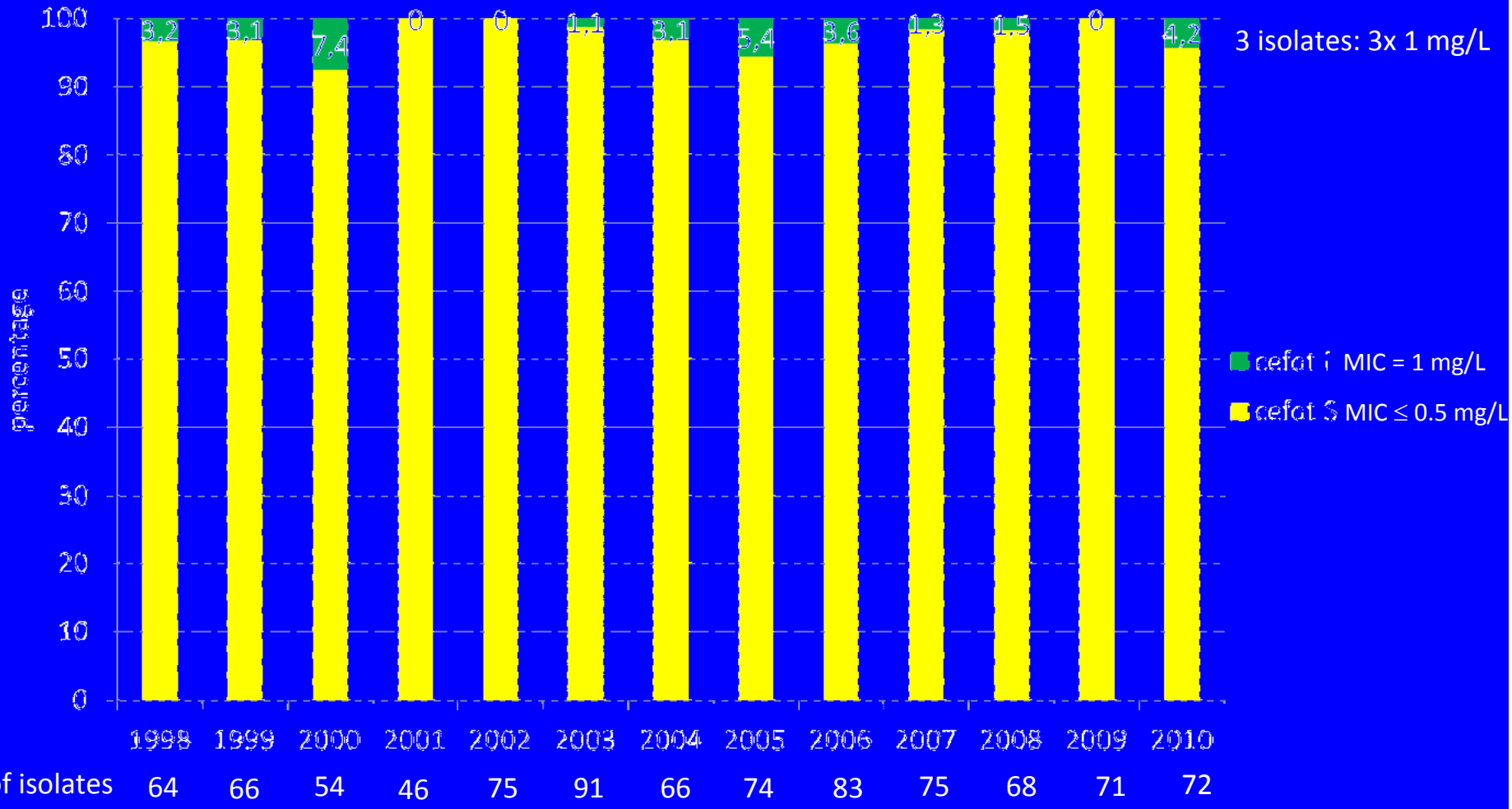


N° of isolates	64	66	54	46	75	91	66	74	83	75	68	71	72

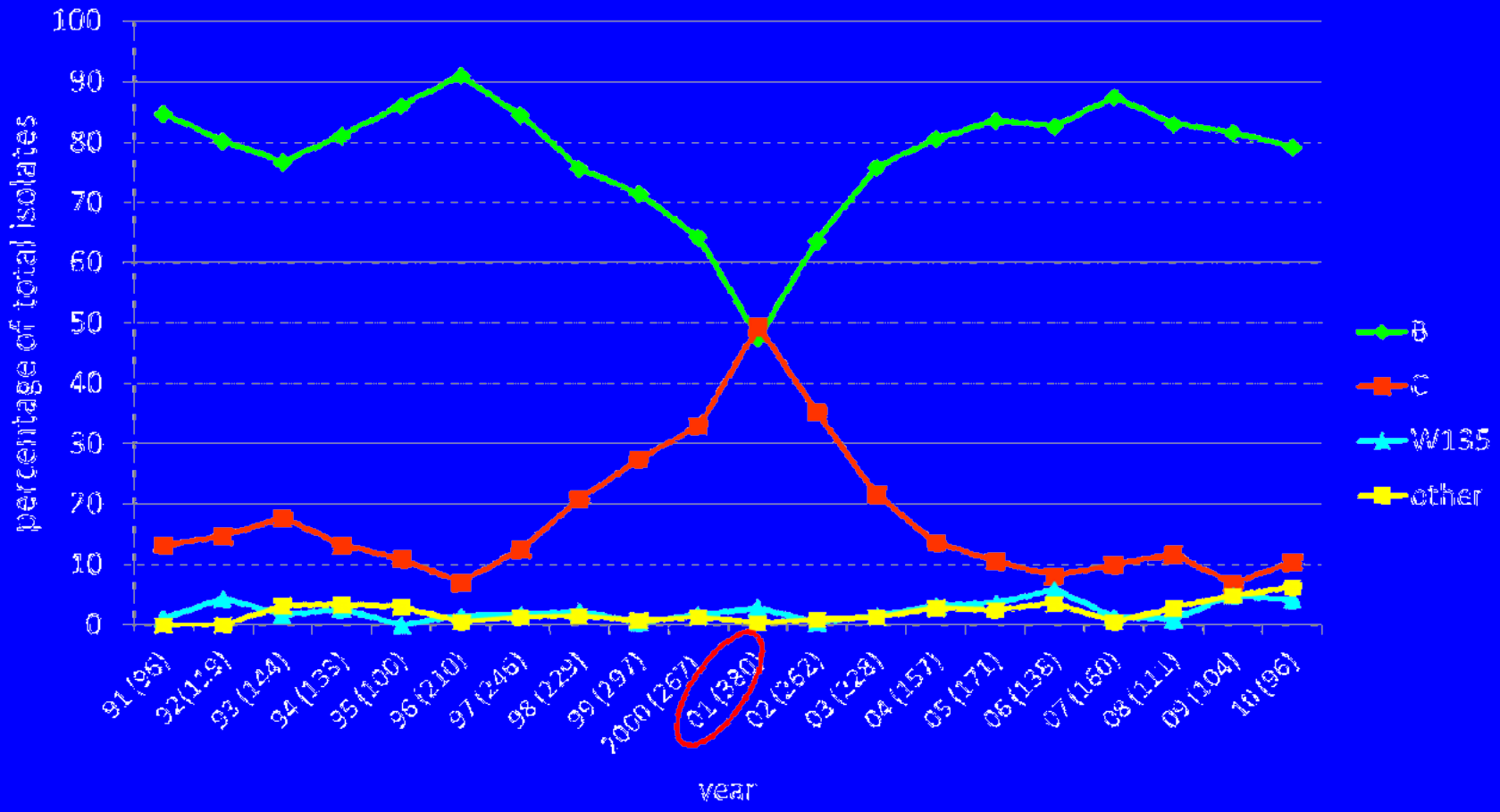
Evolution of penicillin-susceptibility in SGT 19 cerebrospinal fluid isolates



Evolution of cefotaxime-resistance in cerebrospinal fluid isolates of *S. pneumoniae* (Belgium 1998 – 2010)

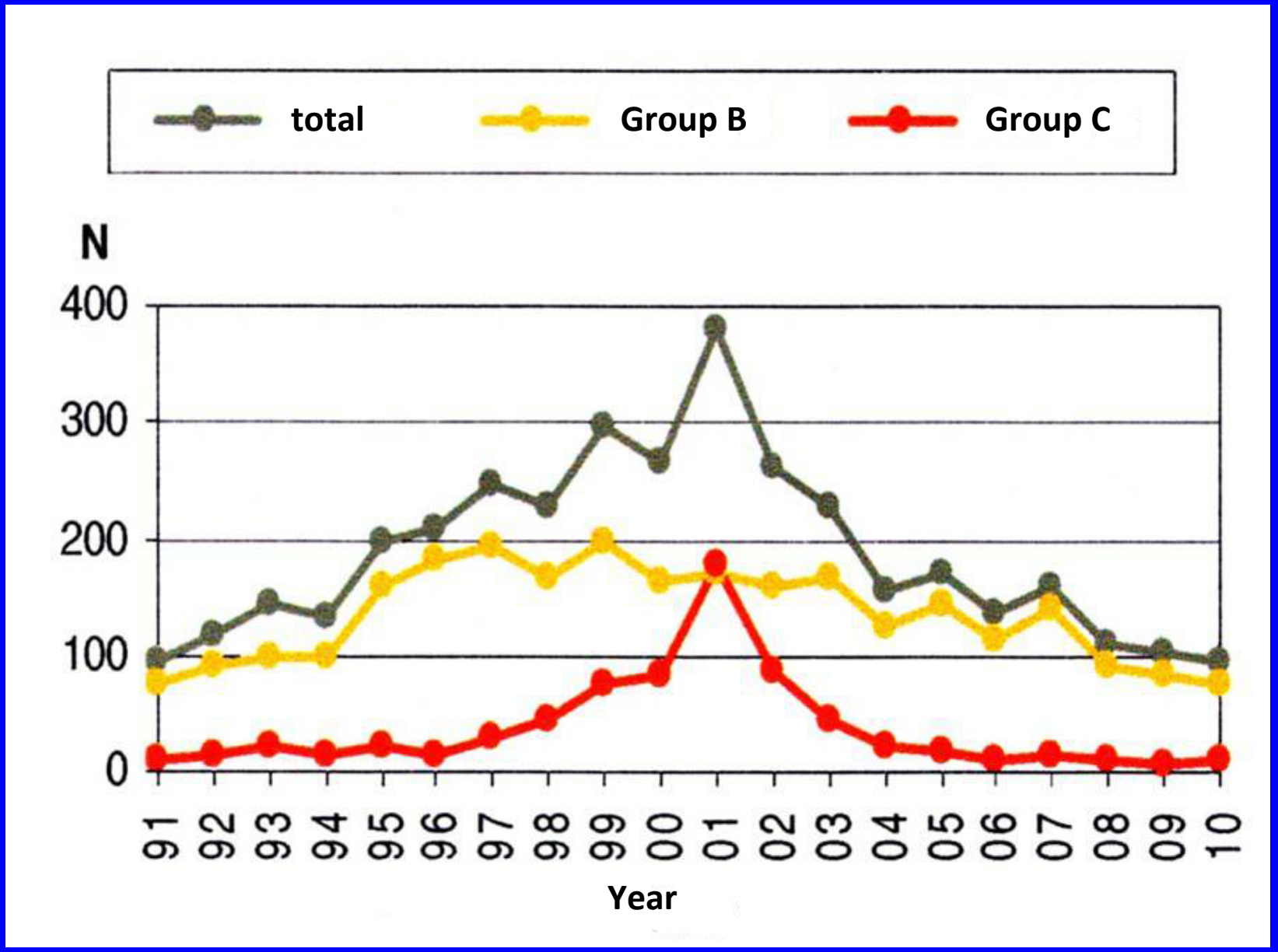


Evolution of number ( ) and serogroups of invasive *Neisseria meningitidis* isolates (Belgium 1991 – 2010)



S. Bertrand, Nat Ref Lab, WIV-ISP, 2010

Evolution of number of meningococcal infections in Belgium (1991 – 2010)



S. Bertrand, Nat Ref Lab, WIV-ISP, 2010

Susceptibility to antibiotics of 88 invasive isolates of *Neisseria meningitidis* (Belgium 2010)

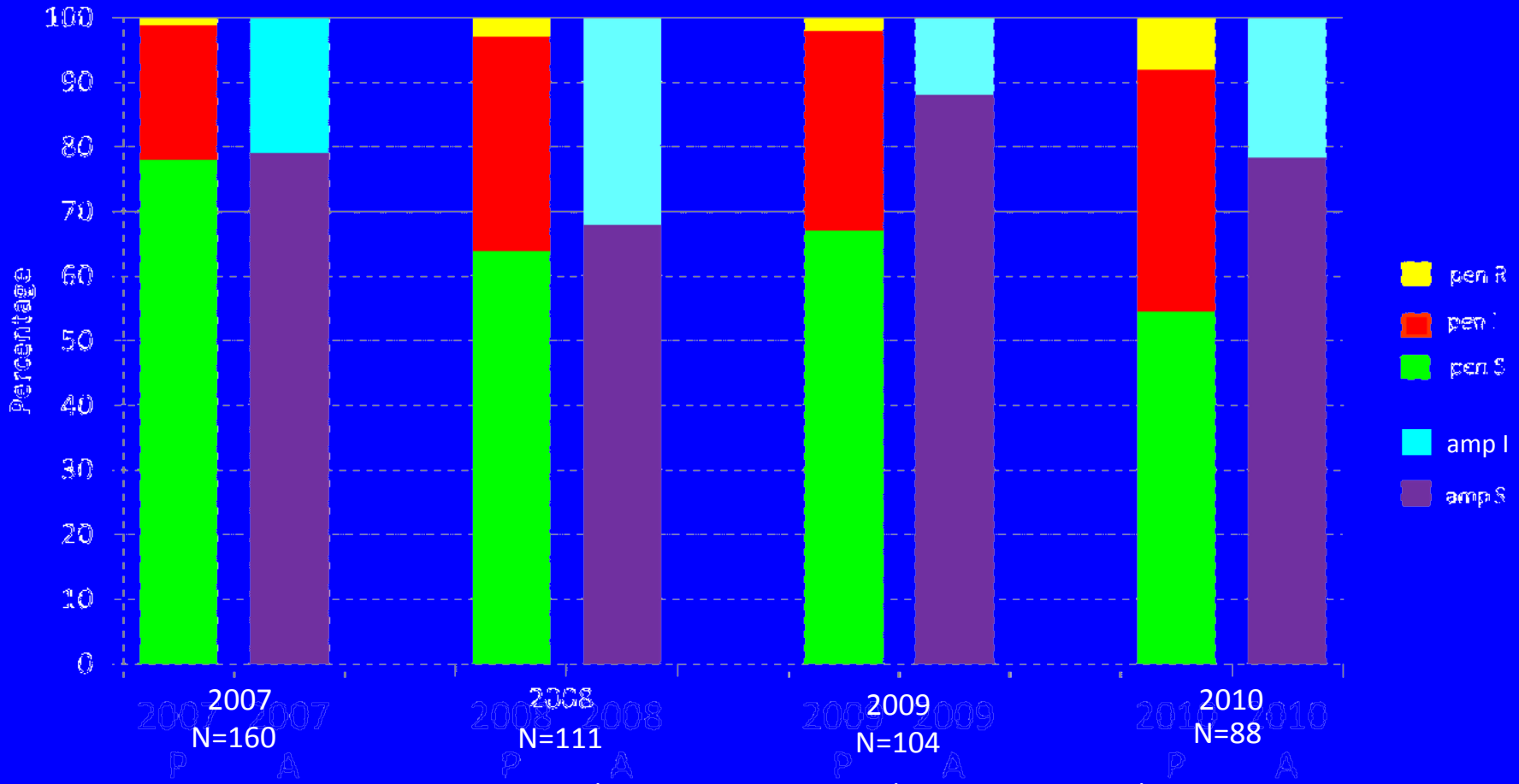
antibiotic	range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	% susceptibility (breakpoint CLSI Jan 2011)
penicilline G	0.008 – 0.5	0.06	0.25	54.5 (≤0.06 mg/L*)
ampicilline	0.016 – 0.25	0.032	0.25	78.4 (≤0.12 mg/L)
cefotaxime	0.002- 0.016	0.008	0.016	100 (≤0.12 mg/L)
chloramphenicol	0.5 -2	1	2	100 (≤2 mg/L)
ciprofloxacine	0.002 -0.008	0.004	0.008	100 (≤ 0.03 mg/L)
rifampicine	0.004 – 8	0.016	0.12	100 (≤0.5 mg/L)
azithromycine	0.016 - 1	0.25	0.5	100 (≤2 mg/L)

*37.5% I (0.12≤MIC≤0.25 mg/L),
7.9% R (MIC≥0.5 mg/L)

non susceptible: 29x group B, 6x group C, 4x W135, 1x group Y

S. Bertrand, Nat. Ref. Lab WIV-ISP, 2010

Evolution of penicilline and ampicilline susceptibility of invasive isolates of *Neisseria meningitidis* (Belgium 2007 – 2010)



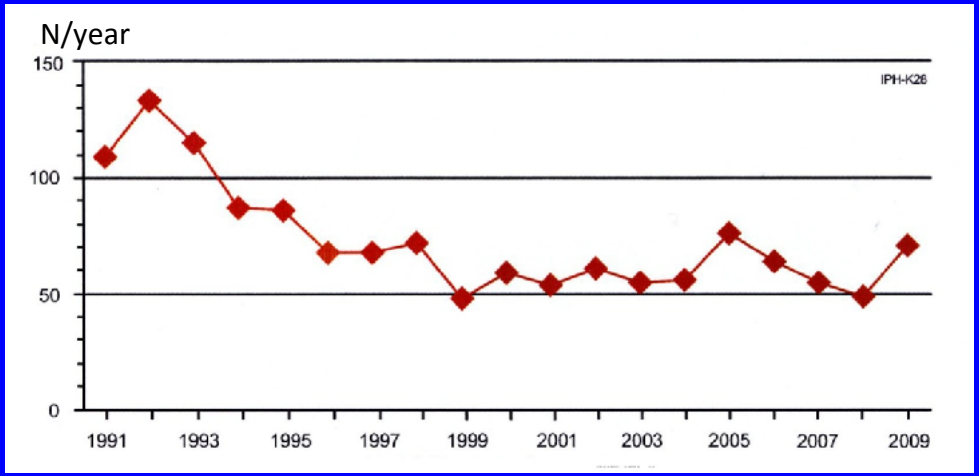
penicilline: S ≤0.06 mg/L I: 0.12 – 0.25 mg/L R: ≥0.5 mg/L

ampicilline: S ≤0.12 mg/L I: 0.25 – 1 mg/L R: ≥2 mg/L

S. Bertrand, Nat Ref Lab, WIV-ISP, 2010

Haemophilus influenzae type B (Hib) invasive infections

- Hib is responsible for 95% of all invasive *H. influenzae* infections
- Routine immunization has resulted in a remarkable decline in serious Hib disease and has eliminated Hib meningitis among vaccinated infants and young children



- 74 isolates in 2009
  - → 90.5% from blood, 5.4% from CSF, 2.7% from BAL, 1.4% from pleural fluid
  - → 13.7% children <5y, 5.5% children 5-<15y, 2.8% adults 15-<45y, 35.6%: adults 45-<65y, 42.4% elderly
- no evidence that non type b strains have replaced Hib as a cause of invasive infections
- worldwide three million episodes of invasive Hib infections and 400,000 deaths (WHO)

Human *Listeria monocytogenes* infections in Europe

- In 2006, 23 Member States reported 1,583 cases → incidence rate of 0.3 cases/100.000 population; highest incidence rates in Denmark (1), Finland (0,9) and Luxembourg (0,9)

- Between 1999 and 2006: statistically significant increase were noted in Germany, Ireland, the Netherlands, Spain and the UK
  - Increase occurred almost exclusively in patients ≥ 60 years of age and dit not appear to be linked to any single common source outbreak (predominantly sporadic in nature)
  - Numbers of cases among patients < 60 years, those with infections of the central nervous system and those associated with pregnancy have remained similar.

Eurosurveillance, 2008, Vol 13, p 1-5

Human *Listeria monocytogenes* infections in Europe

FIGURE 3

Incidence of human listeriosis by age group, European Union, 2006

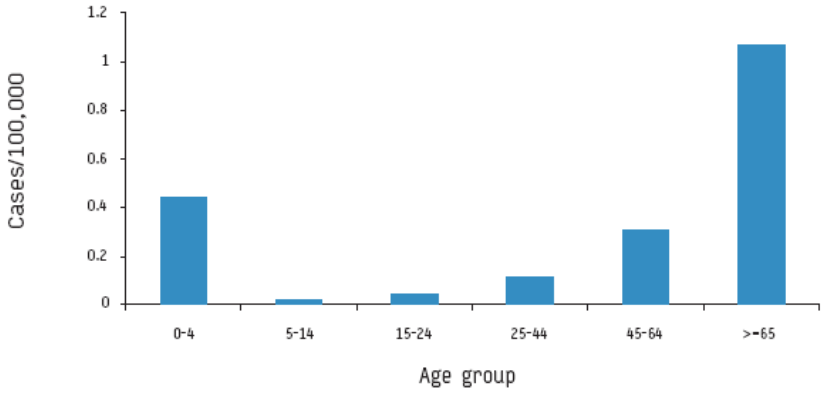
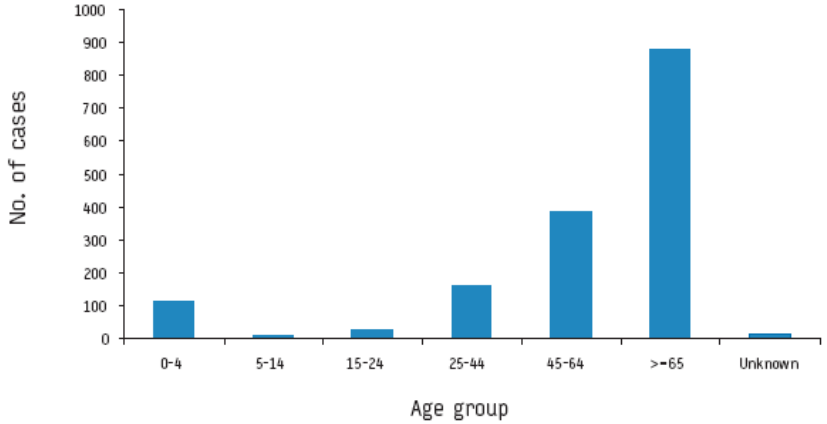


FIGURE 4

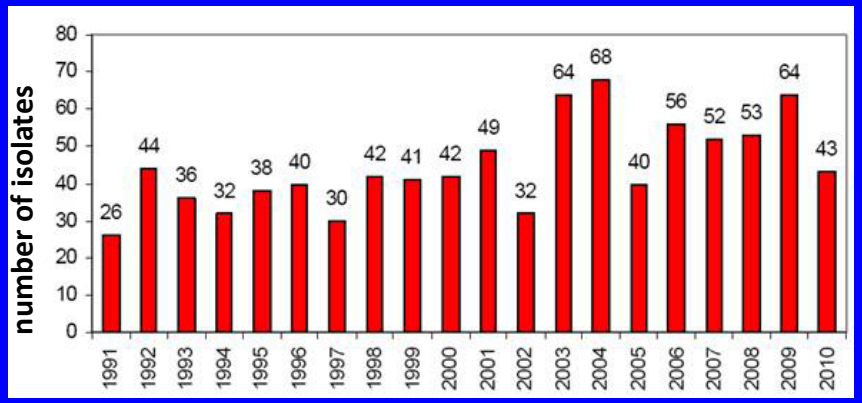
Number of cases of human listeriosis by age group, European Union, 2006



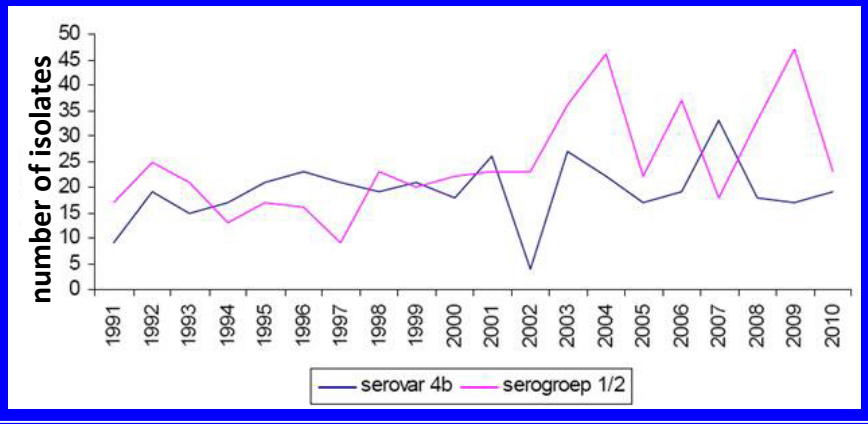
Eurosurveillance, 2008, Vol 13, p1-5

Listeria monocytogenes surveillance in Belgium (1991-2010)

- Evolution of the number of clinical isolates



- Evolution of serogroup ½ and serovar 4b among clinical isolates



Listeria monocytogenes surveillance in Belgium (1991-2010)

- In 2010: 43 clinical isolates:
  - Serogroup ½ = 23x
    - Serovar ½ a = 16x
    - Serovar ½ b = 6x
    - Serovar ½ c = 1x
  - Serogroup 4 = 20x
    - Serovar 4b = 19x
    - Serovar 4e = 1x

Repartition of invasive Listeria infections among type of infection in Belgium (2006-2010)

	2006 (N=56)	2007 (N=52)	2008 (N=53)	2009 (N=64)	2010 (N=43)
Perinatal infections	7%	11.5%	9.4%	3.1%	14%
Non-perinatal infections					
CSF	10.7%	9.2%	5.6%	4.7%	7%
Blood + CSF	0%	6.2%	9.4%	9.4%	2.3%
Blood	78.6%	70.1%	68%	76.5%	67.4%
Other	3.6%	3%	7.6%	6.2%	9.3%

Antibiotic susceptibility of 43 isolates of *L. monocytogenes* (Belgium, 2010)

antibiotic	Mic range (µg/ml)	MIC90 (µg/ml)	%I	%R
amoxicillin	0.25 – 1	0.75	0	0
vancomycin	1 – 2	2	0	0
erythromycin	0.094 – 0.5	0.38	0	0
chloramphenico l	3 – 6	6	0	0
	0.38 – 6	1	2.3	4.6
ciprofloxacin	0.002 – 0.023	0.023	0	0
co-trimoxazol				

M. Yde, Nat Ref Lab, WIV-ISP, 2010